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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,472	CHARETTE, MARC F.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-32,34-38,43,44,46,48 and 51-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-32, 34-38, 43, 44, 46, 48, and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 5, 2007 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed April 5, 2007 is acknowledged. Claims 1-26, 33, 39-42, 45, 47 and 49-50 are cancelled. Claims 27-32, 34-38, 43, 44, 46, 48, and 51-53 are pending and under examination.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

4. Applicant's arguments filed on April 5, 2007 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Oath/Declaration

5. The request of new oath/declaration is withdrawn in response to Applicant's amendment to the claims.

Specification

6. The objection to the specification is withdrawn in response to Applicant's amendment to the claims.

Oath/Declaration

7. The requirement of a new oath/declaration is withdrawn in response to Applicant's amendment to the specification and the claims.

Specification

8. The objection to the specification as introducing new matter is withdrawn in response to Applicant's amendment to the specification.

Claim Rejections/Objections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 27-38, 43, 44, 46, 48, 51-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for up-regulating the expressions of N-CAM and L1 in NG108-15 cells and increasing dendritic arbors of 7-14 DIV cultured hippocampal neurons with OP-1 (BMP-7) protein of SEQ Id NO:2, does not reasonably provide enablement for general methods for reducing memory dysfunction associated with damaged hippocampal tissues and caused by permanent or transient global ischemia comprising administering a structurally

ill-defined morphogen merely comprising a conserved C-terminal seven-cysteine skeleton that is at least about 60% identical and 70% homologous to residues 330-431 of human OP-1 (SEQ ID NO:2) or fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims, for the reasons made of record in Paper No.20060907, and as follows.

Applicant argues that the rejection based on the premise that the effects of OP-1 on hippocampal neurites in vitro cannot be extrapolated to the effects in vivo is false because the prophetic examples 1-14 described in the specification provide enough guidance to enable one of skill in the art to practice the claimed invention and a prophetic example (example 18) in US 6723698 is enabling to anticipate the instant claims (p. 7-8 of the response). Applicant argues that the reference of Charron et al. is not related to the rejection because the examiner fails to provide any evidence that Shh is required for practicing the claimed invention. Further, Applicant argues that the examples shown in the reference contradict the role of gradients of Shh and BMP having a function in treating a damaged tissue and for synapse formation because OP-1 induces dendrite formation in cultured hippocampal neurons without the presence of Shh and any gradient of OP-1. Applicant further argues that even if OP-1 gradients were required for dendritic growth, the specification teaches the morphogen intraventricularly administered into the brain would be expected to from a

gradient (p.8-9 of the response). Applicant's arguments have been fully considered but they are not persuasive.

In contrast to Applicant's assertion on p. 7-8 of the response with respect to failure of extrapolating in vitro data to the in vivo, it is noted that different diseases have different causes and the in vitro condition is optimized for neuronal survival and non-neuronal NG108-15 cells, indicating that a skilled artisan can not predict the results in different diseases based on such in vitro data. Based on the disclosure and prior art, Applicant is enabled for a method of enhancing neuronal survival in the hippocampus in vivo by administration of OP-1 to a subject. However, Applicant is not enabled for a method of reducing memory dysfunction associated with damaged hippocampal tissue because issues related to memory function are complex, unpredictable and involve more than neural survival and dendritic development. It requires reconnecting the damaged neurons and reestablishing synaptic plasticity and cognitive function of the brain. In contrast, Applicant fails to demonstrate that administration of OP-1 or related fragments as recited in the claims to a patient or animal suffering from memory dysfunction associated with damaged hippocampal tissue can enhance reconnecting the damaged neurons and reestablishing synaptic plasticity and cognitive function of the brain, which are required for reducing memory dysfunction. Thus, it is unpredictable whether OP-1 promotes synaptogenesis in the hippocampus in vivo can reduce memory dysfunction associated with damaged hippocampal tissue.

In response to Applicant's argument on p. 8-9 of the response with respect to the irrelevance of the reference of Charron, the examiner asserts that the reference of Charron is related to the rejection. As previously made of record, Charron et al teach that different concentrations of morphogens have different gradient effects on axonal guidance and subsequently affect synapse formation. For example, Sonic hedgehog (Shh) needs to coordinate with BMP in cell fate determination and axon guidance during neural development. Shh functions as a chemoattratant and BMP7:GDF7 heterodimers mediate a chemorepellent activity to collapse growth cone in the developing spinal cord, indicating that axonal guidance and synapse formation require a balance of concentration of different morphogens. However, Applicant fails to provide sufficient guidance as to enable one of skill in the art on how to use a morphogen with limited homology to OP-1 and related fragments as recited in claims 27-32, 34, 35, 46 and 48 in reducing memory dysfunction in vivo caused by different mechanisms as recited in claims 27, 46, 48 and 51-53. A balance of concentration of different morphogens, such as a balance between Shh and BMP, is important for regulating synapse connection between axons and dendrites in the developing spinal cord, indicating that a balanced concentration of different morphogens is also important for synapse formation and synaptic plasticity in neural development in the hippocampus. However, Applicant fails to provide sufficient guidance as to how to achieve a balance of different morphogens in enhancing synapse formation and establishing synaptic plasticity in damaged hippocampal tissue in vivo and subsequently reducing memory dysfunction. In addition, OP-1 intraventricularly

administered to the brain simply diffuses to different brain regions. It is unpredictable whether intraventricular administration of OP-1 at any concentration in the brain would achieve a balance of different morphogens that can enhance synapse formation and establishing synaptic plasticity that are required for reducing memory dysfunction. Therefore, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would require undue experimentation to practice the claimed invention as it pertains to a method for reducing memory dysfunction associated with damaged hippocampal tissue.

In addition, claims 34-35 recite a mature form of human OP-1. However, the claims no longer contain a defined structure for OP-1. Although Applicant describes the useful form of morphogens including the mature form of OP-1, Applicant fails to specify which specific form would be useful in the claimed method as filed in the original specification since there are many possible mature forms of OP-1 described in US 5266683 (see col. 8-9, Table I). Since the specification fails to define a specific structure for a mature form of human OP-1, it is unpredictable what a mature form of OP-1 might be and could be used in the claimed method. Further, the Wands factors have been considered and those relevant to enablement of the instant invention have previously been discussed. Accordingly, the rejection of claims 27-38, 43, 44, 46, 48, 51-53 under 35 U.S.C. §112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 27-32, 34-38, 43, 44, 48, 51-53 are rejected under 35 U.S.C. 102 (e) as being anticipated by U. S. Patent No. 6723698 (Rueger et al. issued on April 20, 2004, effective filling date September 25, 1997), for the reasons made of record in Paper No.20060907, and as follows.

Applicant argues that US6723698 does not teach damaged hippocampal tissue caused by permanent or transient global ischemia (i.e. as it relates to claims 27-32, 34-38, 43 and 44), biocompatible microspheres (i.e. as it relates to claim 44; p.9 of the response), neurotoxins such as ibotenic acid, ammonia and formaldehyde (i.e. as it relates to claim 46), and malnutrion or metabolic disorders (i.e. as it relates to claims 48, 51-53; p.10 of the response).

In contrast to Applicant's assertion on p. 9 of the response, US6723698 ('698) teaches hypoxia and ischemia-reperfusion, which is a permanent or transient global ischemia (i.e. as it relates to independent claim 27; see col.36, lines 36-67). '698 also teaches administration of OP-1 to prevent neuronal cell death caused by ischemia (as it relates to claim 27; see col.36 example 11),

traumatic brain injury (col. 53, example 20). The hippocampal tissue damage is an intrinsic result of global ischemia and cerebral ischemia. In addition, as previously made of record, '698 teaches biocompatible microspheres such as PEG, bioresorbable polymers or liposomes to deliver the OP-1 (i.e. as it relates to claim 44; see col. 21, lines 5-25). Further, as previously made of record, '698 also teaches administration of OP-1 to prevent neuronal cell death caused by mechanical/chemical trauma/neurotoxin including ethanol (see col. 30, example 6), malnutrition, metabolic disorders (i.e. as it relates to claims 48, 51-53; see col.1, lines 42-50). Thus, the rejection of claims 27-32, 34-38, 43, 44, 48, 51-53 under 35 U.S.C. 102 (e) for being anticipated by U. S. Patent No. 6723698 is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 27-32, 34-38, 43, 44, 46, 48, 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rueger et al. (US Patent No. 6723698, issued on April 20, 2004, priority September 25, 1997) in view of Contestabile et al. (J. Neurosci. Res. 1990. 26: 483-7), Simonsen et al. (Scand J. Work Environ. Health. 1994. 20: 1-12) and Gillette-Guyonnet et al. (Am. J. Clin. Nutr. 2000. 71:637S-642S). The rejection under Kern et al. (Neurotoxicity. 1993. 14: 319-27) is withdrawn in response to Applicant's amendment to the claims.

Rueger et al. ('698) is as set forth in Paper No.20060907 and paragraph 10. However, Rueger et al. ('698) do not teach ibotenic acid, ammonia, formaldehyde as neurotoxin (i.e. as it relates to claim 46) and do not teach neuronal loss caused by anorexia (i.e. as it relates to claim 53).

Contestabile et al. teach ibotenic acid and ammonia as a neurotoxin to cause neuronal damage (i.e. as it relates to claim 46; see p. 483, abstract). Simonsen et al. teach formaldehyde as a neurotoxin to cause neuronal damage (i.e. as it relates to claim 46; see p. 637S, abstract). Gillette-Guyonnet et al. teach that weight loss is associated with Alzheimer's diseases, which is characterized by hippocampal neuronal loss and damage, and anoxreia is also associated with AD (i.e. as it relates to claim 53; see p. 319, abstract). However, Contestabile et al., Simonsen et al., and Gillette-Guyonnet et al. do not teach reducing memory loss associated with damaged hippocampal tissue by an OP-1 morphogen.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to protect neurons against neuronal damage due to the toxicity of neurotoxin such as ibotenic acid, ammonia and formaldehyde by administration of OP-1 since ibotenic acid, ammonia and formaldehyde has been shown to cause neurotoxic effects on neurons and OP-1 has been shown to be neuroprotective on neuronal damage caused by chemical/physical trauma/neurotoxin. The person of ordinary skill in the art would have been motivated to administer OP-1 to the damaged hippocampus caused by neurotoxin such as ibotenic acid, ammonia and formaldehyde because OP-1 has been shown to enhance neuronal survival in the hippocampus. One of ordinary skill in the art would have expected success in reducing the neurotoxicity caused by ibotenic acid, ammonia and formaldehyde by using OP-1.

In addition, It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to reduce neuronal damage caused by malnutrition due to anorexia by administration of OP-1 since anorexia has been shown to be related to AD, which is characterized as hippocampal damage and OP-1 has been shown to be neuroprotective on neuronal damage caused by malnutrition as taught by Rueger et al. ('698). The person of ordinary skill in the art would have been motivated to administer OP-1 to the damaged hippocampus caused by malnutrition or anorexia because OP-1 has been shown to enhance neuronal survival in the hippocampus. One of ordinary skill in the art would have expected success in reducing the neuronal damage caused by malnutrition or anorexia by using OP-1.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 34 and 35 recite the broad recitation " a mature form of human OP-1" with no structural charateristics, and the claims 34 and 35 depend from the claims recite residues 330-431 and residues 30-292 of human OP-1 of SEQ ID NO:2, which

are the narrower statements of the range/limitation. In other words, the base claims recite specific structures of OP-1 (i.e. specific residues that are required for the morphogen to be used in the claimed method), while several possible mature forms of OP-1 have been described in US 5266683 (see col. 8-9, Table I). Therefore, it is unclear what a specifically mature form of OP-1 that Applicant intends to use and within the scope the claims.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
Chang-Yu Wang, Ph.D.
June 11, 2007

RCH
ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER